UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/819,105	03/28/2001	Kalyan Handique	10255-014-999	4325

20583 7590 11/28/2003

PENNIE AND EDMONDS
1155 AVENUE OF THE AMERICAS
NEW YORK, NY 100362711

EXAMINER	
GORDON, BRIAN R	

ART UNIT	PAPER NUMBER
1743	

DATE MAILED: 11/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/819,105	HANDIQUE ET AL.	
	Examiner	Art Unit	
	Brian R. Gordon	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14-22 and 24-53* is/are rejected.

7)☐ Claim(s) *13 and 23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Specification

1. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-9, 28-34, and 39-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Southgate 5,863,801.

Southgate et al. discloses an invention relates to a device that incorporates a cassette further comprising (1) a hollow body having a top side, an exterior, an interior, at least one slot for the placement of the cassette, and at least one well for the placement of a sample container. Additionally, the cassette includes a means for moving the cassette from or into the caddy, as well as a means for activating the input transfer sample bar. The preferred device also comprises an air nozzle in communication with means for accessing, storing, or generating pressurized air, and a means for sealing sample input channels of the cassette. Furthermore, the device includes valve actuators located in the interior for opening and closing valves in the

cassette, and one or more pump actuators for moving fluid in or out of fluid chambers in the cassette. The device of the present invention also preferably includes a magnet, a power supply, a user interface, and a bar-code reading means. Preferably, the device of the present invention also comprises a sensor means in the slot or well, which signals that the slot or well is occupied when a cassette or sample container has been respectively inserted therein. In another embodiment, the device of the present invention further comprises a memory means. In yet another embodiment, the device further comprises a separating means for separating the strip from the remainder of the cassette. The separating means is preferably a knife having a heating means in communication thereto, the use of which seals both the strip and the remainder of the cassette.

The device is for nucleic acid extraction from one or more biological samples, preferably comprising a removable cassette that is insertable into a slot in the device. Preferably, the device includes slots for four different cassettes that can be run concurrently, serially, or in a staggered fashion. The device preferably includes a physical enclosure covering its enclosed mechanisms, which comprise the internal chemical, electromechanical, electrical, electronic, and computer assemblies, as well as a power supply. The device preferably includes an operator interface, which includes a suitable display of symbol- or language-based information, such as a liquid crystal display, and a keyboard for inputting information, which can be numeric, alphabetical, or alphanumeric. The device also preferably includes a bar-code scanner as well as software for processing such information. Further software that is preferably included

with the device include instrument control software dedicated to the bar-code reader as already noted, the sample loader sequencer and sample transfer sequencer, the cassette assay sequencer, the batch transporter loader sequencer, calibration of fluid movement, and regulatory requirements satisfaction control. Software is also preferably included in the device for user help functions, manual sample identification input, and error handler, wherein any perturbations or other perceivable error events are recognized and stored for output with a final result report. Power source used for operating the inventive device is standard line voltage of 100 to 240 Volts, alternating current, at a frequency of 50 Hz to 60 Hz.

The device preferably includes the cassette that further comprises: (1) one or more sample entry ports located on the input transfer sample bar that are serially and respectively in communication with the same number of wells of the device, wherein the ports are also in communication with input sample storage reservoirs of the cassette; (2) one or more reaction flow-ways that are serially and respectively in communication via fluid exchange channels with the same number of sample input storage reservoirs; (3) fluid chambers in communication with the fluid exchange channels, wherein fluid chambers are supply chambers for reagents, reservoirs for samples, or reaction chambers; (4) valves for controlling the flow of fluids in the fluid exchange channels; and (5) a sample transfer/storage strip having at least one of the fluid chambers that is in communication with a reaction flow-way.

The user interface preferably provides information to the laboratory technician who is to use the device. The technician preferably will be notified by the user interface

of any warnings, error conditions, instructions for operating the device, as well as instructions provided in response to inquiries presented by the technician. For example, a red light/green light signal can be employed to signal when the device is ready to be operated, such as, for example, leave to load more sample containers. Operator commands such as "READY FOR SAMPLE LOADING," "SAMPLE LOADER FULL," "LOAD CASSETTES," "REMOVE CASSETTES," "PUSH START BUTTON TO INITIATE BATCH SAMPLE PREPARATION," "INSERT NEW BATCH SAMPLE CARRIER," "REMOVE BATCH SAMPLE CARRIER" are preferably displayed by the user interface at suitable times in the operation of the device.

The controller of the operations of the device and thus of the contained cassette preferably is a microprocessor. However, it can also be a simpler device comprised of timers, switches, solenoids and the like. The important feature of a controller is that it directs the activation of the means for impelling a fluid from one fluid chamber to another, and opens or closes valves as appropriate, according to a pre-set or programmable schedule that results in the operation of a nucleic acid preparation protocol, such as the protocol outlined below.

4. Claims 1-6, 8-9, 28-34, 39, and 41-45 are rejected under 35 U.S.C. 102(b) as being anticipated by by Soane et al. US 5,750,015.

Soane et al. discloses an invention that relates to moving charged particles such as charged molecules within a medium in response to a plurality of electrical fields which are applied simultaneously and/or sequentially along the medium containing the charged molecules in order to move the charged molecules in a precise and controlled

fashion. The movement of the electrical fields can be accurately controlled both spatially and temporally. Charged particles in the medium can be moved so as to separate particular types of charged particles away from one another and thus provide a highly defined analytical technique. Further, specific charged molecules can be moved towards each other into precisely defined regions (stable postions) in order to react particular types of molecules together in a synthesis or sequencing protocol employing lateral branches (passages) to a central trench, where movement in the lateral branches is controlled by electrodes to provide for electrokinetic (electrical signals) movement.

As a device for conducting reactions (e.g., sequencing synthesis methods), the different fields connected to the movement area can be applied so as to move specific types of charged molecules into contact with other types of charged molecules in order to react the molecules and carry out any number of different reaction protocols (processing requests). The electrical connections contacting the movement area are preferably in the form of intelligent integrated circuitry which is interactive with a computer system (host computer) capable of activating the fields in any given manner so as to create precise types of separation of molecules for analysis or combinations of molecules for reaction.

Referring now to the drawings, in FIG. 1, a specific embodiment of an analytical device useful in carrying out methods of the present invention is shown schematically. The Card 1 includes a hollowed-out area or Trench 2 which, again, may be of any size but for convenience might preferably be produced on the credit card size Card 1 so that

the Trench 2 is about 1-10 centimeters in length and has a depth of about 5-200, usually 5-150, particularly 5-25 microns.

The Trench 2 is filled with a medium 3 which may be a buffer solution, polymeric solution, surfactant mutlicellular dispersion or gel of the type generally used in connection with analytical separation techniques. For example, polyacrylamide gel used in PAGE analytical procedures is extremely useful in connection with the present invention. A variety of materials may be used alone or in combination with other materials which materials should provide frictional resistance to the charged particles and not substantially interfere with the electrical fields.

The electrodes 4-10 are either simultaneously biased by the application of different voltages to each of the electrodes 4-10 or sequentially biased by the application of different voltages which are biased in a programmed manner. The electrodes 4-10 are biased or fired simultaneously or sequentially and the magnitude of the field applied across any given electrode or all of the electrodes is adjustable over any given range at any given instant in time.

Trench 2 may be filled with a medium 3 which is preferably in the form of a polyacrylamide gel material or a buffered solution with or without a synthetic polymer; alone or in combination with a surfactant. In order to carry out the electrophoresis or movement of charged particles for synthesis or sequencing, a buffer will be supplied, at reservoirs at the termini of the trenches and lateral branches or means can be provided for connecting the ends of the trenches and lateral branches to reservoirs for allowing for the flow of liquid during operation of the device. After the gel has been added, a

sample of material is then placed at one end of the medium and time-dependent and/or variable position-dependent voltages are applied to the electrodes. Although it is possible to supply the voltage to the electrodes in a variety of different manners, it is most preferable to supply the voltage so that electrical fields are sequentially activated one after another in a single direction so as to provide a traveling electrical wave which moves in a single direction along the trench. This wave or waves can be made to move at a variety of speeds depending upon the particular types of molecules being separated. As the wave or waves move, charged particles will be drawn through the medium within the Trench 2. Charged particles which tend to move more quickly will, of course, be drawn through the medium by moving waves which move quickly along the length of the trench. However, particles which tend to move slowly through the medium 3 can only be moved by waves which move generally slowly through the medium 3.

It is preferable for the electrodes to be connected to an electronic computer which computer has programmed software dedicated to providing the moving waves or voltage profile along the Trench 2. Various different types of software can be provided so as to obtain the best possible resolution with respect to separating various types of charged particles from one another.

In yet a more sophisticated embodiment of the invention, the computer software which is connected to the electrodes can be made interactive with an optical detection device such as an ultraviolet or fluorescence spectrometer. The spectrometer can be focused singly or at various points along the medium 3 in the Trench 2. As the ultraviolet spectrometer reads different types of particles being moved to different

portions of the medium 3, the information can be sent to the computer which can adjust the speed of the waves or voltage distribution profiles being generated in order to more precisely fine-tune the resolution of the charged particles being moved through the medium 3.

Trench 2 can be fashioned so that it has a plurality of branches thereon. Each of the branches of the Trench 2, along with the trench itself can be filled with a buffer solution. Thereafter, the base of each of the branches can be supplied with a particular charged reactant material. The charged reactant materials can then be moved into contact with one another by utilizing the moving electrical wave generated by the computer. Accordingly, sophisticated computer programs can be set up in order to provide for synthesis or sequencing protocols of a variety of different types of molecules. For example, different nucleotides can be reacted to form DNA and different amino acids can be reacted to form proteins. These reactions can be carried out at greatly increased speeds as compared with conventional mechanical technologies. In addition to increased speeds, the yield is vastly improved due to the precision with which the reactants can be moved. It is possible to carry out DNA or protein sequencing procedures.

The embodiment in FIG. 2 provides for mixing and separation of molecules, so that reactions may be carried out between different reactants, mixtures separated and components combined with other materials, assays carried out by mixing a component of a sample with one or more assay reagents, and the like. In FIG. 2, Card 20 has a network which includes a central hollowed-out area or trench 22 with lateral hollowed

areas or trenches serving as branches, with an upper branch 24, a middle branch 26 and a lower branch 28. The branches 24, 26 and 28 cross and interconnect with the central trench 22, forming reaction sites 30, 32 and 34, respectively. The central trench 22 has entry port 36 and exit port 38 for introduction and removal of samples, mixtures, reactants and the like. Each of the branches have similar ports, the upper branch 24, having entry and exit ports, 40 and 42, respectively, the middle branch entry and exit ports, 44 and 46, respectively, and the lower branch, 48 and 50, respectively. The ports 36 and 38 communicate with reservoirs 37 and 39, respectively. Similarly, reservoirs could be provided proximal to the ends of the branches, if desired. The reservoirs have sufficient capacity for performing the necessary operations and providing the necessary ions for movement of the components of interest during the operation. Alternatively, the reservoirs may be connected to pumps for pumping liquid into the reservoirs to maintain the reservoirs at a substantially constant composition.

The Card 20 has plated thereon a plurality of electroplated finger-like electrodes 60-64. The electrodes are biased in accordance with the needs of the purpose for which the Card 20 is being used. Thus, the electrodes 60 and 60' can be biased to move a sample from entry port 36 to reaction site 30. Once the sample is at or adjacent the reaction site 30, a reactant may be introduced into entry port 40 and by biasing electrodes 63 and 63', the reactant moved to the reaction site 30 to permit mixing and reaction at reaction site 30. By allowing the sample and reactant to incubate for sufficient time for reaction to occur, either under an appropriate electrical field or no field, one may then bias electrodes 60 and 60' to move the reacted sample down the

central trench 22. The process of movement and reaction may be permitted at each reaction site, where depending upon the system, separation of the reaction mixture may result between reaction sites or all of the reaction mixture may be simultaneously moved to the next reaction site. If desired, components may be removed from the reaction mixture, where the reaction mixture has undergone separation between reaction sites. When a component reaches a reaction site, the electrodes controlling the branch may be activated to provide a bias which will move the component into the respective branch and out of the central trench 22. Finally, the reaction mixture may be moved to terminal site 66. Where a detectable label has been provided, as in an assay sequence, one may determine the signal from the label. Alternatively, one may withdraw the components of the reaction mixture through an appropriate port, not shown.

In addition to the electrodes controlling the central trench 22 and branches 24, 26 and 28, electrodes 63 and 63' are provided which provide for an electrical bias along the central trench, which electrodes may be used as described above or for moving sample and reactants in various directions by appropriately biasing individual electrodes, with different pairs of electrodes being used. For example, by appropriately biasing electrodes 61' and 63 one may bring a reactant into the central channel to the position where electrode 63 is placed. One may provide for a plurality of electrodes along the central trench 22, as described above, so that fine control of movement of the components.

5. Claims 1-9, 28-34, and 39-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Ramsey US 6,033,546.

Ramsey discloses a microchip laboratory system and method provide fluid manipulations for a variety of applications, including sample injection for microchip chemical separations. Capillary electrophoresis and electrochromatography are performed in channels formed in the substrate. Analytes are loaded into a four-way intersection of channels by electrokinetically pumping the analyte through the intersection, followed by switching of the potentials to force an analyte plug into the separation channel. The invention relates generally to miniature instrumentation for chemical analysis, chemical sensing and synthesis and, more specifically, to electrically controlled manipulations of fluids in micromachined channels. Operations that are performed in typical laboratory processes include specimen preparation, chemical/biochemical conversions, sample fractionation, signal detection and data processing. To accomplish these tasks, liquids are often measured and dispensed with volumetric accuracy, mixed together, and subjected to one or several different physical or chemical environments that accomplish conversion or fractionation. In research, diagnostic, or development situations, these operations are carried out on a macroscopic scale using fluid volumes in the range of a few microliters to several liters at a time. The invention provides the tools necessary to make use of electrokinetic pumping not only in separations, but also to perform liquid handling that accomplishes other important sample processing steps, such as chemical conversions or sample partitioning. By simultaneously controlling voltage at a plurality of ports connected by channels in a microchip structure, it is possible to measure and dispense fluids with great precision, mix reagents, incubate reaction components, direct the components

towards sites of physical or biochemical partition, and subject the components to detector systems. By combining these capabilities on a single microchip, one is able to create complete, miniature, integrated automated laboratory systems for analyzing or synthesizing chemicals.

Shown in FIG. 1 is an example of a microchip laboratory system 10 configured to implement can entire chemical analysis or synthesis. The laboratory system 10 includes six reservoirs 12, 14, 16, 18, 20, and 22 (stable positions) connected to each other by a system of channels 24 micromachined into a substrate or base member (not shown in FIG. 1), as discussed in more detail below. Each reservoir 12-22 is in fluid communication with a corresponding channel 26, 28, 30, 32, 34 and 36, of the channel system 24. The first channel 26 leading from the first reservoir 12 is connected to the second channel 28 leading from the second reservoir 14 at a first intersection 38. Likewise, the third channel 30 from the third reservoir 16 is connected to the fourth channel 32 at a second intersection 40. The first intersection 38 is connected to the second intersection 40 by a reaction chamber or channel 42. The fifth channel 34 from the fifth reservoir 20 is also connected to the second intersection 40 such that the second intersection 40 is a four-way intersection of channels 30, 32, 34, and 42. The fifth channel 34 also intersects the sixth channel 36 from the sixth reservoir 22 at a third intersection 44.

The materials stored in the reservoirs preferably are transported electrokinetically through the channel system 24 in order to implement the desired analysis or synthesis. To provide such electrokinetic transport, the laboratory system 10 includes a voltage

controller 46 capable of applying selectable voltage levels (electrical signals), including ground. Such a voltage controller can be implemented using multiple voltage dividers and multiple relays to obtain the selectable voltage levels. The voltage controller is connected to an electrode positioned in each of the six reservoirs 12-22 by voltage lines V1-V6 in order to apply the desired voltages to the materials in the reservoirs. Preferably, the voltage controller also includes sensor channels S1, S2, and S3 connected to the first, second, and third intersections 38, 40, 44, respectively, in order to sense the voltages present at those intersections.

In most applications envisaged for these integrated microsystems for chemical analysis or synthesis it will be necessary to quantify the material present in a channel at one or more positions similar to conventional laboratory measurement processes. Techniques typically utilized for quantification include, but are not limited to, optical absorbance, refractive index changes, fluorescence emission, chemiluminescence, various forms of Raman spectroscopy, electrical conductometric measurements, electrochemical amperiometric measurement, acoustic wave propagation measurements.

6. Claims 1-6, 8-9, 28-34, 39, and 41-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Parce et al. US 5,885,470.

Parce et al. disclose a microfluidic devices are provided for the performance of chemical and biochemical analyses, syntheses and detection.

The invention also provides a method for directing movement of a fluid within a microfluidic device. The method comprises providing a microfluidic device having at

least first and second intersecting channels disposed therein. Each of the first and second intersecting channels has a fluid disposed therein, wherein the at least first and second channels have interior surfaces having a surface potential associated therewith, which is capable of supporting sufficient electroosmotic mobility of the fluid disposed in those channels. The device also includes at least first, second, third and fourth ports disposed in the substrate, wherein the first and second ports are in fluid communication with the first channel on different sides of the intersection of the first channel with the second channel, and the third and fourth ports are in fluid communication with the second channel on different sides of the intersection of the second channel with the first channel. A voltage gradient is then applied between at least two of the first, second, third and fourth ports to affect movement of said fluid in at least one of the first and second intersecting channels.

The microfluidic device may exist alone or may be a part of a microfluidic system which can include: sampling systems for introducing fluids, e.g., samples, reagents, buffers and the like, into the device; detection systems; data storage systems; and control systems, for controlling fluid transport and direction within the device, monitoring and controlling environmental conditions to which the fluids in the device are subjected, e.g., temperature, current and the like. A schematic illustration of one embodiment of such a system is shown in FIG. 1. As shown, the system includes a microfluidic device 100. The device, and particularly the reagent wells or ports of the device are electrically connected to voltage controller 110, which controls fluid transport within the device. An example of a particularly preferred voltage controller is described in, e.g., U.S. patent

application No. 08/691,632, filed Aug. 2, 1996, and incorporated herein by reference in its entirety for all purposes. Detection of the output of the device is carried out by detector 120. Both detector 120 and voltage controller 110 are connected to computer 130, which instructs voltage controller in the selective application of varying voltage levels to the various ports of the device 100. The computer also receives and stores detection data from detector 120, and is typically appropriately programmed to perform analysis of those data.

In operation, fluid transport within these devices is carried out by applying a voltage gradient along the path of desired fluid flow, thereby electroosmotically driving fluid flow along that path. Some methods for affecting electroosmotic fluid flow incorporate a "floating port" fluid direction system, where a sample fluid in one reservoir and channel is drawn across the intersection of that channel with another channel, by applying a voltage gradient along the length of the first channel, i.e., by concomitantly applying a voltage to the two ports at the ends of the first channel. Meanwhile, the two ports at the ends of the second channel are allowed to "float," i.e., no voltage is applied. The plug of sample fluid at the intersection is then drawn into the second channel by applying a potential to the electrodes at each end of the second channel. While this method allows injection of a sample of one fluid into a different channel, a number of disadvantages remain. In particular, leakage can occur at the sample intersection as a result of fluid convection, e.g., fluid from one channel "bleeds over" into the other channel. This bleeding over effect can result in imprecise and nonreproducible fluid movements, which can be problematic where one desires more precise fluid control.

However, in preferred aspects, the fluid control and direction systems incorporated into the systems of the present invention apply voltages to multiple reservoirs, simultaneously. In the case of a fluid being transported in a first channel through an intersection with a second channel, this permits the introduction of constraining or directing flows from the second channel, whereby one can precisely control the level of fluid flow in a given direction. This simultaneous application of potential to multiple ports allows for specific control of the fluid at the intersection of the channels, reducing or eliminating the convective effects that are generally seen with floating port methods. For example, a fluid of interest flowing through an intersection of two channels may be precisely constrained by flowing additional fluids from the side channels by appropriate, simultaneous application of voltages to the reservoirs or ports at the ends of those channels, resulting in the fluid of interest being maintained in a "pinched" conformation which prevents bleeding over into the side channels. The volume of the fluid of interest contained within the intersection is readily calculable based upon the volume of the intersection, and also is readily reproducible. Further, this volume of fluid can be readily diverted to one of the intersecting channels by appropriate modulation of the potentials applied at each reservoir or port.

7. Claims 1-9, 28-34, and 39-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Handique et al. US 5,750,015.

Handique et al. discloses an invention that relates to microfabrication and biological reactions in microfabricated devices, and in particular, movement and mixing of biological samples in microdroplets through microchannels. The description of the

invention involves I) the design of microscale devices (comprising microdroplet transport channels, reaction chambers, electrophoresis ports, and radiation detectors) using silicon and glass substrates, II) the creation (or definition) of microdroplets having a discrete size, III) movement of discrete microdroplets using a surface-tension-gradient mechanism in which discrete microdroplets are differentially heated and propelled through etched channels, IV) flow control with sealed valves, and V) mixing of biological samples for reactions. The invention contemplates microscale devices, comprising microdroplet transport channels having hydrophilic and hydrophobic regions, reaction chambers, gas-intake pathways and vents, electrophoresis modules, and detectors, including but not limited to radiation detectors. In some embodiments, the devices further comprise air chambers to internally generate air pressure to split and move microdroplets (i.e. "on-chip" pressure generation).

Electronic components are fabricated on the same substrate material, allowing sensors and controlling circuitry to be incorporated in the same device. The present invention contemplates a method for moving microdroplets, comprising: (a) providing a liquid microdroplet disposed within a microdroplet transport channel etched in silicon, said channel in liquid communication with a reaction region via said transport channel and separated from a microdroplet flow-directing means by a liquid barrier; and (b) conveying said microdroplet in said transport channel to said reaction region via said microdroplet flow-directing means. It is not intended that the present invention be limited by the particular nature of the microdroplet flow-directing means. In one embodiment, it comprises a series of aluminum heating elements arrayed along said transport channel

and the microdroplets are conveyed by differential heating of the microdroplet by the heating elements. In one embodiment, said first microdroplet comprises nucleic acid and said second microdroplet comprises a nuclease capable of acting on said nucleic acid. In this embodiment, it is desirable to enhance the mixing within the merged microdroplet. This can be achieved a number of ways. In one embodiment for mixing, after the conveying of step (d), the flow direction is reversed. It is not intended that the present invention be limited by the nature or number of reversals. If the flow direction of said merged microdroplet is reversed even a single time, this process increases the mixing of the reactants. The present invention also contemplates a method for restricting fluid flow in a channel, comprising: a) providing: i) a main channel connected to a side channel and disposed within a substrate, ii) meltable material disposed within said side channel and associated with a heating element, and iii) a movement means connected to said side channel such that application of said movement means induces said meltable material to flow from said side channel into said main channel; b) heating said meltable material such that said meltable material at least partially liquifies; and c) applying said movement means such that said liquified meltable material flows from said side channel into said main channel. While the present invention is not limited by the movement means, in one embodiment the movement means is forced air. Successful mixing, can be confirmed by characterization of the product(s) from the reaction. Where product is detected, mixing has been at least partially successful. The invention contemplates, in one embodiment, using electrophoresis to confirm product formation.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 10-12, 14-22, 24-27, 35-38, and 46-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soane et al as applied to claims 1-6, 8-9, 28-34, 39, and 41-45 above, and further in view of Handique et al.

Soane et. al. does not disclose that the device specifically functions in response to sub-sequence and sub pattern controls or that the device comprises a meltable material.

It would have been obvious one of ordinary skill in the art at the time of the invention to program the computer system of Soane et al. to include sub-pattern responses as well as the metable material in the channels could be used to selectively control the flow of fluid in the channels.

Allowable Subject Matter

12. Claims 13 and 23 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The following is a statement of reasons for the indication of allowable subject matter: The prior art does not teach nor fairly suggest heating at least on gas micro reservoir communication with the passage.

Conclusion

13. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Chow et al. (,675 and ;089)Anderson et al., Dubrow et al. (,175 and ,343) Parce et al. (,974 and ,389), Chow, Mathies et al., and Quake et al. disclose microfluidic devices.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian R. Gordon whose telephone number is (703) 305-0399. The examiner can normally be reached on M-F, with 2nd and 4th F off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on 703-308-4037. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9310.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0661.

brg

Jill Warden
Supervisory Patent Examiner
Technology Center 1700